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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/856,200

01/03/2003

Peter D. Kwong

54203-H-PCT-US/JPW/SHS

3857

7590

05/15/2006

John P White
Cooper & Dunham
1185 Avenue of the Americas
New York, NY 10036

EXAMINER

TALAVERA, MIGUEL A

ART UNIT

PAPER NUMBER

1656

DATE MAILED: 05/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/856,200

Applicant(s)

KWONG ET AL.

Examiner

Miguel A. Talavera

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 February 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 27, 28, 37 and 38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date November 5, 2004.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,21,27,28,33,34,36-38,42,44-49,53,55-59,61,80,81,83-86,90,91 and 94.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 1,21,33,34,36,37,42,44-49,53,55-59,61,80,81,83-86,90,91 and 94.

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DETAILED ACTION

Status of the Application

1. In response to the previous Office action, a written restriction requirement (mailed on September 20, 2005), Applicants filed a response/election received on February 26, 2006. Claims 1, 21, 27, 28, 33, 34, 36-38, 42, 44-49, 53, 55-59, 61, 80, 81, 83-86, 90, 91 and 94 are pending in the instant Office action.
2. Applicant's election with traverse of Group II, claims 27, 28, 37 and 38, in the reply filed on February 26, 2006 is acknowledged. The traversal is on the ground(s) that because Groups II and VI share claims 27 and 28, it cannot "be the case that claims of Groups II and VI lack at least one common technical feature." This is not found persuasive. According to PCT Rule 13.2 unity of invention exists only when there is a shared same or corresponding special technical feature among the claimed inventions. As stated in the previous Office Action, the inventions of Groups II and VI do not have unity of invention because each of the inventions has a *different* special technical feature. The special technical feature of Group II is a method for identifying or designing a compound capable of binding to a portion of HIV-gp120, including a compound that binds to the CD4 binding site on HIV-gp120. The special technical feature of Group VI is a method for identifying or designing a compound capable of binding to a portion of HIV-gp120, including a compound that binds to the chemokine receptor binding site on HIV-gp120. It is acknowledged that Groups II and VI share claims 27 and 28, they nonetheless have a different special technical feature that is not shared. Consequently the inventions of Groups II and VI do not have unity of invention.

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Also, according to PCT Rule 13.2 unity of invention exists only when the shared same or corresponding special technical feature is a contribution over the prior art. As noted below, the invention of Group II is obvious in view of the prior art and thus, the invention of Group II is not a contribution over the prior art. Consequently the inventions of Groups II and VI do not have unity of invention.

3. Claims 1, 21, 33, 34, 36, 42, 44-49, 53, 55-59, 61, 80, 81, 83-86, 90, 91 and 94 are withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b), as being drawn to a nonelected invention(s), there being no allowable generic or linking claim. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. Claims 27, 28, 37 and 38 are being examined on the merits.

Priority

5. This application is a 371 national stage application of PCT/US98/23905, filed on November 10, 1998, which is a continuation-in-part and claims the benefit of US Serial Nos: 09/100763, 09/100763, 09/100529, 09/100762 and 09/100521, filed 06/18/1998; US Serial No: 08/976741, filed 11/24/1997; and US Serial Nos: 08/966987, 08/967403, 08/966932 and 08/967148, filed 11/10/1997. The invention finds support in US Serial No: 08/967148 filed on 11/10/1997.

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Information Disclosure Statement

6. The information disclosure statement (IDS) filed on November 5, 2004 has been reviewed, and the references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

7. The listing of references in the specification (pp. 95-99, 122-129, 158-164, 180-183, 194 and 196-198) is not a proper information disclosure statement. 37 C.F.R. § 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and M.P.E.P. § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-1449 or PTO-892, they have not been considered.

Sequence Compliance

8. The Examiner can find no sequence listing filed in the instant application.

9. The instant application contains at least one nucleic acid and/or amino acid sequence that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). As such, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990) and 1114 OG 29 (May 15, 1990).

a) The structural coordinates in Figures 53-1 to 53-111, i.e., atoms 1 to 2300, atoms 2496 to 3907, atoms 3909 to 5553 and atoms 5555 to 7277, teach several amino acid sequences since a particular amino acid is assigned to a linear sequence in a particular order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with

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the sequence rules. Labeling using a SEQ ID NO must be inserted into the brief description of the drawings or into the Figure directly.

- b) The sequence alignment in Figures 29D-1 and 29D-2 teaches several amino acid sequences. When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. See M.P.E.P. § 2422.02.

Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in a sequence listing, Applicants must provide (1) a copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Specification/Informalities

10. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---
Method for Identifying Potential Inhibitors of the CD4-GP120 Interaction by Using the X-ray

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Structural Coordinates of the ~~Complex of the~~ Extracellular Domain of Human CD4, HIV-1 Envelope Protein GP120 and the Fab Fragment of Monoclonal Antibody 17B ---

11. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests including of the full name of the source species (i.e. human CD4 and HIV type), for completeness.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 27, 28, 37 and 38 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The claims are indefinite because of the use of the term "portion" or "portion of gp120". Neither the specification nor the claims provides a clear definition of what is intended by the term "gp120" or a "portion" thereof. What characteristics distinguish a "gp120" glycoprotein from any other glycoprotein such that a skilled artisan could identify the intended scope of "gp120." Further, because the specification fails to define a "portion" or what is intended as being encompassed by the term, it is unclear as to that part of a "gp120" that is considered to be a "portion" and that part that is not. Is the term "portion" meant to be interpreted as a single atom? A single amino acid? Ten contiguous amino acids of the primary

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sequence? A particular, localized tertiary structure or fold? Clarification of the metes and bound of the claims is requested.

b. The claims are indefinite because it is unclear as to how a skilled artisan is to determine a binding site, determine whether a compound would fit, and/or design a compound as encompassed by the claims. Are these meant to be purely mental steps, active method steps, or a combination thereof. If they are meant as active method steps, what process or processes are involved in such “determining” or “designing” steps? It is suggested that applicant clarify the meaning of the claims.

Claim Rejections - 35 U.S.C. § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 27, 28, 37 and 38 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The instant claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description requirement is separate and distinct from the enablement requirement. See *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998).

The claims encompass subject matter that is not defined nor appropriately described in the specification. Claims 27 and 28 are directed to a method for identifying or designing a gp120

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associating compound relying on the use of all possible atomic coordinates that can be determined from all possible crystals of a "portion of gp120". Claims 37 and 38 are directed to a computational based method for identifying or designing compound capable to the CD4 binding site relying on the use of a "portion" from all possible atomic coordinates that can be determined from all possible crystals of a "portion of gp120" capable of binding to CD4. However the specification lacks adequate written description to demonstrate to a skilled artisan that applicant was in possession of the claimed invention.

The specification has given no concise definition of the "portion" and said term does not impart any structural limitations on the gp120, crystals and derived atomic coordinates thereof. The specification neither describes nor exemplifies all possible portion of the protein that demonstrates a biological activity and structure characteristic of the protein. There are no requirements as to whether the atomic coordinates of instant method have atoms that are covalently attached or separated by a distance within the radius of gyration of the polypeptide, only that the atomic coordinates represent a "portion" of gp120. Furthermore, the polypeptide "gp120" as recited in the claims lacks a clear and concise structural and functional correlation for the claimed genera of polypeptides. Although Applicants seem to establish that the "gp120" polypeptides encompassed by the broad claims is a reengineered full-length polypeptide from an HIV source for crystallization purposes, there is no clear description (e.g., by sequence identifier, number of amino acid residues or nucleotides, etc). Multiple variants exist in nature (for example, HIV types), more could be generated in the lab, and the claims are not limited to a specific polypeptide sequence. Without identifying and sequencing each variant, there is no way to know what their sequences are. Therefore, applicants have not disclosed, nor does the art

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recognize, the requisite structural and functional* features of all the contemplated amino acid sequence possibilities recited in the instant claims, which are required for selecting a chemical entity that binds gp120 or interrupts the gp120:CD4 interaction, a feature deemed essential to the instant invention.

The Court of Appeals for the Federal Circuit has held that a “written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” UC California v. Eli Lilly, (43 USPQ2d 1398). For claims drawn to a genus, M.P.E.P. § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. M.P.E.P. § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. While M.P.E.P. § 2163 acknowledges that in certain situations “one species adequately supports a genus”, it is also acknowledges that “[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.”

In this case, the specification discloses only a single representative species of structural coordinates comprising a “portion” of gp120, *i.e.*, Figures 52-1 to 51-122, obtained from a single

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representative of a crystalline form comprising a “portion” of gp120, i.e., trimeric complex between fully deglycosylated HIV-1 gp120 construct $\Delta 82\Delta V1/2*\Delta V3\Delta C5$, D1D2 sCD4 and Fab 17b (see Table 2, 4, 5 and 6 at pp.103-106). This single representative crystalline form fails to reflect the variation of polypeptide species, crystalline forms and structural coordinates thereof as encompassed by the claims. Other than this single representative species, the specification fails to describe any additional species by any relevant, identifying characteristics or properties. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Therefore, the claimed genera of gp120 polypeptides, crystalline forms and derived atomic coordinates thereof are widely variant and not defined by a specific correlation between structure and/or function of the polypeptides, crystalline forms thereof and corresponding atomic coordinates representing the widely variant polypeptide forms.

Given the lack of description of a representative number of polypeptides, crystalline forms and atomic coordinates thereof, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention. At best, it simply indicates that one should run tests on a wide spectrum of portions of gp120 in the hope that at least one of them can be isolated, crystallize and lead to a suitable screening three-dimensional model. Inadequate written description that merely identifies a plan to accomplish an intended result “is an attempt to preempt the future before it has arrived” (*Fiers v. Revel*, 984 F.2d 1164,1171 9Fed.Cir. 1993).

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14. Claims 27, 28, 37 and 38 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for *in silico* screening of compounds using the full-set of atomic coordinates or a defined binding pocket within said full-set, as set forth in Figures 52-1 to 51-122, obtained from the X-ray diffraction data of a crystal consisting of the trimeric complex between fully deglycosylated HIV-1 gp120 construct $\Delta 82\Delta V1/2*\Delta V3\Delta C5$, D1D2 sCD4 and Fab 17b (see Table 2, 4, 5 and 6 at pp.103-106), does not reasonably provide enablement for making new crystals consisting of a "portion" of gp120 from which a three-dimensional model can be generated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. To practice the claimed methods to the full extent of their scope would require undue experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See M.P.E.P. § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claims 27, 28, 37 and 38 are so broad as to encompass computer-based screening methods for analyzing the interaction of a candidate compound with a three-dimensional model of any "portion" of gp120, wherein said models are generated through

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X-ray crystallographic analysis. A "portion" can be construed to mean as few as a single amino acid. The broad scope of claimed models is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides variants consisting of portions of gp120 for X-ray crystallographic analysis, including all potential crystals, crystallization conditions and experimental models thereof necessary for such analysis. In this case the disclosure is limited to the crystal containing trimeric complex between fully deglycosylated HIV-1 gp120 construct $\Delta 82\Delta V1/2*\Delta V3\Delta C5$, D1D2 sCD4 and Fab 17b, that, upon X-ray crystallographic analysis, leads into the set of structural coordinates of Figures 52-1 to 51-122.

The nature of the invention: The invention is related to screening for compounds that interact with a three-dimensional structure/model of a protein that is generated either from X-ray diffraction data. For the reasons discussed below, the nature of the claimed invention is highly complex.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art:

Models generated through X-ray diffraction data of a macromolecular crystal

The claim method relies on the art of macromolecular crystallization for identifying or designing associating compounds. A method that relies on data from an unpredictable art such as protein crystallization would require clear and precise guidance for one skilled in the art to reliably use said method. The state of the art at the time of the invention acknowledges a high level of unpredictability for crystallizing a macromolecule. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New

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York, 1999) teaches that “[c]rystallization is usually quite difficult to achieve” (p. 375). Also, Drenth et al. (“Principles of X-ray Crystallography,” Springer, New York, 1995) teaches that “[t]he science of protein crystallization is an underdeveloped area” and “[p]rotein crystallization is mainly a trial-and-error procedure” (p. 1). Even applicants’ own specification acknowledges that crystallizing mammalian species of gp120 is difficult, disclosing that, [The extensive glycosylation and conformational mobility of gp120...pose formidable barriers for crystallization] (p. 69, lines 10-13).

Successful crystallization is aided by knowledge of the macromolecules behavior in terms of solubility, dependence on metal ions for correct folding or activity, interactions with other molecules and any other information that is available. As evidence by Derewenda *et al.* (Acta Crystallogr. D., vol. 62, pages 116-124, 2006) the outcome of macromolecular crystallization is further compounded by the chemical composition of the macromolecule itself, in particular the molecular surface area, and available surface sites that might participate (i.e., crystal contacts) in holding together the three-dimensional array of macromolecules defining the crystal lattice:

“Clearly, the protein’s microscopic surface properties have a critical impact on the thermodynamics and kinetics of crystallization. It follows then that some proteins will crystallize more easily than others and that the amino-acid composition and sequence are more informative with respect to possible crystallization outcome than is normally believed.” (underline added for emphasis, see Derewenda *et al.*)

Applicant’s disclosure echoes such teaching, disclosing that, [Because of the conformational complexity of gp120, we focused on surface modification..] In view of these disclosed teachings, it is highly unpredictable as to whether all crystals of a portion of gp120 can be made using the crystallization conditions as set forth in Table 5 of the specification.

Since our understanding of crystallization mechanisms are still incomplete and the factors of macromolecular structure that are involved in crystallization are poorly understood, to make the macromolecular crystals encompassed by the scope of a portion of gp120, the following must be clear: the preparation and chemical composition of the molecules to be crystallized, and the specific crystallization conditions, including methods and reagents used, that led to the crystallization of that particular specie. Crystallization experiments must be done in order to empirically determine if a macromolecule will crystallize, and preliminary X-ray diffraction experiments must be done in order to determine if the crystalline macromolecule will diffract to the resolution required for analysis. Therefore, precise instruction about how to make macromolecular crystals suitable for structure determination is required so that undue experimentation is not required. A skilled artisan would recognize that it is highly unpredictable to know *a priori* if any other gp120 variant would form crystals having the specified claimed limitations. That is, current macromolecular structure prediction is not accurate enough nor can macromolecule-solvent and macromolecule-macromolecule interactions be modeled with the necessary precision to pinpoint all contributions to the free energy of crystallization, *ab initio* crystallization prediction for macromolecules is not feasible (see Kierzek *et al.*).

Thus, it is the Examiner's position that screening for suitable portion of gp120 leading to diffraction quality crystals, which might lead to a three-dimensional structure/model, would constitute undue experimentation.

In silico screening

At the time of the invention, *in silico* screening methods for identifying compounds that bind to a defined binding pocket were known in the art (see for example, Balaji *et al.* US Patent

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5,579,250 and Itai *et al.* US Patent 5,642,292). While such methods of structure-based screening of compounds using defined target three-dimensional models representative of the natural state of the target are known in the prior art, knowledge of clearly defined target models for the claimed genus of a portion of gp120 is lacking in the specification.

It is well established in the arts of *in silico* screening that obtaining a potential associating species without a clearly defined target three-dimensional model is highly unpredictable. That is, it would appear to be highly unpredictable as to whether all three-dimensional models of a portion of gp120 having unrestricted structure and atomic composition, would be useful for identifying a compound that interact with a gp120 in its functional assembly state. For example, said three-dimensional models would represent non-biologically-relevant representations of gp120 or the gp120:CD4 interaction. It is highly unpredictable as to whether a compound that is identified as binding to such undefined models, i.e., "portion", as encompassed by the claims will also bind to the biologically relevant protein. Searching among any and all possible three-dimensional models for a target model that is suitable for the evaluation, identification or design of a compound is well outside the realm of routine experimentation and predictability in the art of success is extremely low. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus of three-dimensional models in order to use such members.

The amount of direction provided by the inventor; The existence of working examples:

As stated previously, specific guidance and a single working example are disclosed to determine the structure of a polypeptide using X-ray diffraction data or amino acid sequence data. In addition, there is no reduction to practice of the claimed screening method. It follows that

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without such direction in making a defined three-dimensional model, the specification lacks precise guidance for using the claimed invention.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: In order to practice the claimed invention one of skill in the art must generate three-dimensional protein structural variant models of any "portion" of a gp120 from X-ray diffraction data. For the reasons set forth above, there would be an unpredictable amount of experimentation required to practice the claimed invention.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior and current state of the art, and the amount of experimentation required to make all structural coordinates obtained from crystallographic data as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. Claims 27, 28, 37 and 38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Balaji *et al.* (US Patent 5,579,250, Balaji) in view *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004). The claims are drawn to a computational based method for identifying or designing a compound capable of binding a "portion" of gp120 or to the CD4 binding site of gp120 using atomic structure coordinates of a portion of gp120.

Balaji teaches methods of rational drug design via computer modeling. Specifically, columns 11-32 detail the use of atomic coordinates of a receptor - such as a protein - wherein drugs or compounds which interact therewith are designed using structural coordinate data obtained from, e.g., X-ray crystallography. Polypeptide modeling is specifically discussed in column 24, line 50, through column 25, line 26. In columns 11-32, energy minimization, bond angles, etc. are discussed as parameters in said design methods, including those of making and contacting compound with protein. These descriptions are encompassed by the instant methods, only missing the specific structural coordinates as disclosed in Figures 52-1 to 51-122.

In *Gulack* and *Ngai*, the court held that nonfunctional descriptive material in a claim does not distinguish the prior art in terms of patentability. The key factor in analyzing the obviousness of these claims over the prior art is the determination that the computer algorithm

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used to identify compounds that may bind gp120 is a known algorithm and is unmodified. If the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. In this case, the structural coordinates disclosed in Figures 52-1 to 51-122 are nonfunctional descriptive material and the method uses a known unmodified computer algorithm. Data, which are fed into a known algorithm whose purpose is to compare or modify those data using a series of processing steps, do not impose a change in the processing steps and are thus nonfunctional descriptive material. A method of using a known comparator for its known purpose to compare data sets does not become non-obvious merely because new data becomes available for analysis. Nonfunctional descriptive material cannot render non-obvious an invention that would have otherwise been obvious. See MPEP 2106 and Cases 6-7 of the "Report on comparative study on protein three-dimensional structure related claims" of the "Trilateral Project WM4 Comparative studies in new technologies" at www.uspto.gov/web/tws/wm4/wm4-index.htm.

As non functional data used in a known algorithm do not modify any of the processing steps, and simply changing the data to be processed is not beyond the ordinary skill in the art, it would have been obvious at the time of the invention to perform rational drug design as taught by Balaji to result in an compound that interacts with gp120 or a portion of gp120, wherein only nonfunctional descriptive material is additionally present in the claims, which do not distinguish the claimed methods from Balaji according to *In re Gulack* and *In re Ngai*.

16. Status of the claims:

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Claims 1, 21, 27, 28, 33, 34, 36-38, 42, 44-49, 53, 55-59, 61, 80, 81, 83-86, 90, 91 and 94 are pending.

Claims 1, 21, 33, 34, 36, 42, 44-49, 53, 55-59, 61, 80, 81, 83-86, 90, 91 and 94 are withdrawn from consideration.

Claims 27, 28, 37 and 38 are rejected.

No claim is in condition for allowance.

Conclusion

Claims 27, 28, 37 and 38 are rejected for the reasons identified in the numbered sections of the Office action. Applicants must respond to the objections/rejections in each of the numbered sections in the Office action to be fully responsive in prosecution.


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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Miguel A. Talavera whose telephone number is (571)272-3354. The examiner can normally be reached on M-F, 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on (571)272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER

Miguel A. Talavera, Ph.D.
May 3, 2006